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Maternal serum 25-hydroxy vitamin D level in first-trimester pregnancy loss

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ABSTRACT

Aim: Pregnancy loss (abortus) is defined as loss of fetal cardiac beat or expulsion of pregnancy material before 20 weeks. It has many causes such as chromosomal abnormalities, uterine anomalies, infections, and unknown causes. Vitamin D has become one of the new topics of research in many medical fields, as it has relations with other diseases besides bone diseases. In some studies of recurrent pregnancy loss, a low vitamin D level was found. In our study, vitamin D levels were measured in the first-trimester pregnancy loss and normal pregnancy group.

Methods: Patients, single pregnancies with a positive fetal heartbeat, who applied to the pregnant outpatient clinic for the first examination of pregnancy were included in the study, and vitamin D levels were measured at this time. The patients were followed up to the 12th gestational week using the hospital automation system. The groups of normal pregnancy and abortus groups were determined. 25-hydroxy (25-OH) vitamin D levels between 2-96 ng/ml can be detected, while over 30 ng/ml is sufficient, 20-29.99 ng/ml is insufficient, and <20 ng/ml is defined as a low 25(OH)D3 level.

Results: 66 patients were included in the pregnancy loss group, in the follow-up, 63 patients were in the normal pregnancy group. The mean vitamin D level of the individuals included in the study was measured as 7.45±4.64 ng/ml. Levels of vitamin D were 10.04±6.19 in the normal course group and 4.8±1.73 ng/ml in the intrauterine exitus group ($p<0.05$). At a vitamin D level of 6,87 ng/ml, pregnancy loss was expected with 90% sensitivity and 64% specificity.

Conclusion: It is still an important issue to determine the most appropriate level and preconceptional starting and the appropriate dose for maximum benefit for mother and baby, especially in the reproductive period and pregnant. Therefore, large-scale randomized controlled studies of high quality are needed.

Keywords: Abortus, 25-Hydroxyvitamine D3, pregnancy loss

INTRODUCTION

Spontaneous abortus is described as fetal loss before 20 gestational weeks. Definition of abortus by the World Health Organization (WHO) is; loss of a fetus or embryo that weighs less than 500 grams. While spontaneous abortus is the most seen complication of early pregnancy, its incidence decreases as an increases in the gestational week of pregnancy.[1] Incidence is approximately 8-20% of pregnancies.[2]

The risk factors best associated with pregnancy loss are advanced maternal age, history of abortion, and maternal smoking. Smoking large amounts (more than 10 cigarettes per day) increases the risk of pregnancy loss.[3] Alcohol, cocaine, and nonsteroidal anti-inflammatory drug usage is also a risk factor for abortus. Pre-pregnancy body mass index (BMI) below 18.5 or above 25 kg/m2 was associated with infertility and spontaneous abortion.[4] Chromosomal anomalies are found in 50% of the abortus material. While there is an abnormal fetal karyotype in 90% of pregnancies with an empty sac, this rate is 50% at 8-11 weeks and 30% between 16-19 weeks.[1]

Although these reasons are found, this issue is still not fully resolved. Until a few years, 25-hydroxy (25-OH) vitamin D was seen as the 'bone vitamine', but recently it has been found to affect cancer, metabolic syndrome, infections, metabolic and neurological diseases, even pain. In addition, associations with low vitamin D levels and preeclampsia, gestational diabetes mellitus, hyperemezis gravidarum and preterm birth are found.[5,6]

METHODS

This study was produced from the first author's specialization thesis in gynecology and obstetrics numbered as 10507811 and titled "Maternal serum 25-hydroxy vitamin D

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level in first-trimester pregnancy loss". It is aimed to compare vitamin D levels in first-trimester pregnancy loss with those of individuals who did not experience pregnancy loss.

Approval for this thesis study was obtained from Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Education Planning and Coordination Department (Date 24.01.2014, Decision No. 22). This study had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2013.

Patients, single pregnancies with the positive fetal heartbeat, who applied to the pregnant outpatient clinic for the first examination of pregnancy were included in the study. Patients under the age of 18 and over 35 years of age, those with a history of recurrent abortion, pregnancies using assisted reproductive techniques, thyroid disorders, a history of thrombophilia, diabetes mellitus, patients with antiphospholipid syndrome, and those using vitamin D supplements were not included in the study.

All participating pregnant women were informed about the study and obtained informed verbal consent. Pelvic and physical examinations of all cases were performed, and age, obstetric history, and family history were recorded. In addition, the weight and height of the patients were measured and recorded. The gestational week was calculated to the last menstrual period and biometric measurements made with Toshiba Aplio 500 7.5 Mhz vaginal probe for ultrasonography were calculated. From the patients with a positive fetal heartbeat and who met the study criteria, 2 ml of morning fasting blood sample was taken into an EDTA-free biochemistry tube with a vacutainer from the antecubital vein under sterile conditions centrifuged at 4000 rpm for 10 minutes. The serum samples were stored at -80°C in the Biochemistry Laboratory until the study. stored in the refrigerator.

The patients were followed up to the 12th gestational week using the hospital automation system. The group without pelvic pain and vaginal bleeding until the 12th gestational week was defined as the normal healthy group. Pregnancy loss was defined as patients whose fetal heart rate was negative before the 12th week or whose pregnancy material was completely or partially discarded due to vaginal bleeding.

25(OH)D3 levels in blood samples of selected patients were studied on Elecsys 2010 autoanalyzer (Roche Diagnostics, Mannheim, Germany) by electrochemiluminescent immunoassay (ECLIA) method using original reagents (05894913, Roche Diagnostics, Mannheim, Germany). Results were calculated as ng/ml. (1 ng/mL is equivalent to 2.496 nmol/L.) With this method, 25(OH)D3 levels between 2-96 ng/ml can be detected, while over 30 ng/ml is sufficient, 20-29.99 ng/ml is insufficient, and <20 ng/ml is defined as a low 25(OH)D3 level.

Statistical Analysis

IBM SPSS Statistics 16.0 (IBM Corp. Released 2007. IBM SPSS Statistics for Windows, Version 16.0. Armonk, NY: IBM Corp.) program was used for statistical analysis and calculations. Statistical significance level was accepted as $p<0.05$. The conformity of the continuous variables in the study to the normal distribution was evaluated with the Kolmogorov-Smirnov test. In addition, number (n) and percentage values were given for categorical variables such as the result of pregnancy follow-up, and smoking status obtained within the scope of the study.

Differences between groups according to the course of pregnancy in terms of age, BMI, and gravida were evaluated by an independent t-test. In addition, vitamin D levels were categorized and the relationship between the groups was evaluated with the chi-square test. Finally, the appropriate cut-off value was determined by finding the sensitivity and specificity values for the outcome of pregnancy loss for the vitamin D level.

RESULTS

A total of 472 patients with positive fetal heartbeat at the first pregnancy examination and meeting the study criteria were included in the study. Pregnancy results of 15 patients could not be reached in the follow-up. While 66 patients were included in the pregnancy loss group in the follow-up, 330 patients remained in the pregnancy group with a normal course. 63 patients were selected from the normal pregnancy group by randomization according to the demographic characteristics of the other group.

The mean vitamin D level of the individuals included in the study was measured as 7.45±4.64 ng/ml. Levels of vitamin D were 10.04±6.19 in the normal ongoing group and 4.8±1.73 ng/ml in the intrauterine exitus group($p<0.05$).

When individuals were separated according to age, weight, and body mass index, no significant difference was found between vitamin D levels ($p>0.05$).

Vitamin D levels were classified as levels according to the kit studied; when <20 ng/ml low, 20-29.99 ng/ml deficient levels and >30 ng/ml levels are considered normal and vitamin D levels are recategorized,

Since the number of individuals in some compartments was less than 5 in the evaluation, the vitamin D levels were reclassified as <20 ng/ml and 20 ng/ml and above and reevaluated according to the pregnancy follow-up results;

There was no significant relationship between these vitamin D levels and pregnancy outcomes($p>0.05$). In Table 3; the cut-off value for vitamin D was mentioned for the pregnancy loss group. At a vitamin D level of 6,87 ng/ml, pregnancy loss was expected with 90% sensitivity and 64% specificity.

Table 1. Descriptive values of study groups

Study groups	Healthy group n=63		Pregnancy loss group (n=66)		P
Variables	Mean	Min-max	Mean	Min-Max	
Age (year)	26.58±4.01	19-34	24.12±3.89	18-33	NS
Gravidity	1.57±0.75	1-3	1.41±0.7	1-5	NS
Body mass index (kg/m^2)	25.09±3.42	18-33	24.96±4.46	19-42	NS
Smoking status	61 non-smoker	2 smoker	62 Non-smoker	4 smoker	NS
Full covered Clothing	22 full-covered	41	21 full-covered	45	NS

NS: not statistically significant($p\geq0.05$)

Table 2. The relationship between the outcome of pregnancy follow-up and vitamin D levels

Level of vitamin D (ng/ml)	Number of patients N	
	Normal	Intrauterine exitus
Low (<20)	56	57
Deficiency(20-29.99)	5	8
Sufficient(>30)	2	1

Table 3. Cut-off values of vitamin D levels in pregnancy loss group

Cut-Off	Sensitivity	Spesificity
6,78	0,892	0,644
6,87	0,908	0,644
6,96	0,908	0,630

DISCUSSION

Vitamin D has become one of the new topics of research in many medical fields, as it has relations with other diseases besides bone diseases.

Although the levels of vitamin D in women vary, in the first trimester, Korean women's median vitamin D level is 9.22 ng/ml, which is probably related to low vitamin D intake.[7] On the other hand, the serum 25(OH)D3 level in all women between 13-44 in the USA was 23 ng/ml (95% confidence interval; 22-24).

Serum 25(OH)D3 levels were higher in pregnant women than nonpregnant women. In our study, the average level of vitamin D was 7.45 ng/ml, and 85.6% of the pregnant women had a vitamin D level below 20 ng/ml and it was found to be at the insufficiency level.

As in other studies, no difference was found between vitamin D levels according to age. In one study, young age, low socioeconomic status, pregnancy, and not using late trimester vitamin D supplements were also found to be independent factors. In our study, the first trimester values were examined, and those who used any vitamin D supplements were not included in the study. Therefore, we think that the low vitamin D levels in our study are due to both insufficient intake and not using any supplements.

Although sunlight is the strongest source of vitamin D in summer, the importance of special supplements or fortified foods increases in northern latitudes (40°N). It is included in diet recommendations in most European countries, America, and the world.[8,9] It should be taken at a daily dose of 1,800-4,000 IU to maintain the 25(OH)D3 level at 75-110 nmol/l and to see optimal benefits.[10] Supra physiological toxic levels are above 150 nmol/L. In our study, the rate of pregnant women with optimal vitamin D levels (≥20 ng/ml /50 nmol/L) was 14.4%.

Vitamin D is thought to have immunomodulatory and anti-inflammatory effects by regulating the production and function of neutrophil degranulation products and cytokines. Various cells in the immune system have vitamin D receptors and are modified with vitamin D.[11] Although vitamin D is responsible for suppressing the acquired immune system, it also increases the innate immune response. In addition, it reduces the production of inflammatory cytokines such as IL-1,6, and TNF in cellular immunity.

Active 1.25(OH)D3 is synthesized in human decidual cells. Therefore, most studies show that vitamin D is acquired in fetal-maternal encounters during gestation and is involved in the innate immune response.[12-14] In addition, myometrial contractility is also dependent on calcium release, which is regulated by vitamin D.

The human placenta synthesizes everything needed for vitamin D signals, such as VDR, RXR, CYP27B1, and CYP24A1. Weisman et al.[15] found that human placental and decidual tissues synthesize 1.25(OH)D3 and 24.25(OH) D3. Supporting these findings, cultured human primary syncytiotrophoblasts and decidual cells produce 1,25(OH) D3 and secrete the active form into the culture medium. With an increased amount of 1,25(OH)D3, the transcription of CYP27B1 is decreased in human cytotrophoblasts and syncytiotrophoblasts, while transcription of CYP24A1 is increased.[16] VDR antagonists reduce 1,25(OH)D3-induced CYP24A1 levels.

Insulin-like growth factor (IGF-1) is a key regulator of fetal growth and hydroxylation of 25(OH)D3 in cultured placental cells.[17] 1,25(OH)D3 granulocyte-macrophage colony-stimulating factor 2 (GMCSF-2) increases cAMP while inhibiting TNF-a, IL-6.

A decrease in infection rates and cell death were found with vitamin D treatment, possibly due to increased cAMP levels.[14] This finding supports that vitamin D supplementation reduces infection during pregnancy. Although the effect of infection in recurrent abortions has not been proven, the infection mechanism may be effective in abortion.

Vitamin D and calcium metabolism change during pregnancy. Calcium passes from the mother to the fetus through the placenta. In rats, the placenta passes 25(OH) D3 and 24.25(OH)D3 but not 1.25(OH)D3.[18] Although transplacental transport has not been studied in humans, the maternal-to-fetal transmission of vitamin D is facilitated by the greater availability of 1,25(OH)D3 in the maternal circulation than in the fetus.[19] The synthesis of 1,25(OH)3D increases in the kidney during pregnancy. However, vitamin D levels in pregnant women were insufficient in our study. Transplacental transmission in humans has not been studied, and fetal levels in pregnant women who already have insufficient amounts of vitamin D are also controversial.

Optimal serum levels and the required amount for pregnancy are unknown.[9,20] Although doses of 400, 800, and 1,600 IU are small and have little effect on vitamin D levels in pregnant women, in a recent randomized controlled trial.[21] Vitamin D initiated at a dose of 4,000 IU/day per week was found to be safe and achieved adequate levels in the mother and newborn regardless of race.[22] Although those who used vitamin supplements were not included in our study, there are doses of 500IU in our country's preparations recommended for pregnancy. It is controversial how adequate this dose is for pregnant women.

Although the trans-placental transmission of vitamin D in humans is unknown, local vitamin D synthesis in the human placenta and decidua, the presence of hydroxylation enzymes, and the presence of the vitamin D receptor have

revealed the importance of this hormone in reproductive function.[23] Recent studies supported this by the detection of the vitamin D receptor in the rat endometrium in the oestrus cycle. Although it is prominent for its local effect, many studies have been carried out in the fetomaternal field because it is a powerful immunoregulatory molecule in various studies.

1,25(OH)2D3 inhibits IL-12 and increases the release of IL-10 in dendritic cells. The cytokine profile shifts to the TH2 phenotype.[24] The possible vitamin D mechanism is locally effective. To demonstrate this, tissue and enzyme studies are needed by taking samples from the endometrium. In this regard, Thota et al.[25] uterine smooth muscle cells are cultured in an inflammatory environment, in culture with monocytes, when vitamin D treatment is given, IL-1b, -6,-13, TNFα, connexin-43, prostaglandin receptor, oxytocin, estrogen receptor a, progesterone receptor A/ In the B ratio, a decrease in the nuclear fraction of p-IkBa and NFkB-p65 in the cytosol was detected. These results show that vitamin D reduces inflammation and inflammation-induced markers and contraction-related factors in uterine smooth muscle via the NFkB pathway. Furthermore, D vitamin D treatment reduces cytokines' synthesis in decidual natural killer cells and reduces inflammation triggered by infection.[26]

A low progesterone A/B ratio means high affinity for progesterone and is responsible for maintaining uterine silence.[27] Thota et al.[25] defined that progesterone receptor A/B ratio decreased with vitamin D treatment. It has been observed that vitamin D also reduces NFkB activity in macrophages, thus inhibiting NFkB-activated inflammation and providing myometrial silence during gestation. These mechanisms explain the effect of vitamin D on both abortion imminens and pregnancy loss. Local mechanisms provide the effect.

The study measured vitamin D levels with the ELISA, RIA, EIA methods on the market or the gold standard HPLC method. When these methods were compared, it was determined that HPLC/mass spectrometry was better than colorimetric methods and there were measurement differences between other methods.

In our study, the sensitivity for the cut-off point of 6.87 ng/ml was 0.908 and the specificity was 0.644. Therefore, the area under the curve is 0.817, may be considered a good test. Sensitivity and specificity values for other cut-off points that can be used should also be reconstructed according to the reference values in the table according to the populations. Cut-off values should be determined according to pregnant women, trimester, and population. The results of our study may depend on the method used and may need to be confirmed by the gold standard HPLC/mass spectrometry.

Normal levels of vitamin D were twice as high in white women as in black women (50-60 mmol/L vs. 20-30 mmol/L, respectively). Absorption through the skin is the main source of vitamin D and UV-B rays are necessary to initiate the cascade. Although melanin is more common in dark skin, absorption is reduced in very dark skins as it does not pass UV-B.[28] In our study, vitamin D levels were similar in general, which may be because the population is from the same race.

Low vitamin D levels can be caused by limiting skin exposure due to cultural and religious beliefs. For example, in the study of Holmes VA et al.[29] veiled women in the Victorian region of Australia, although sunlight is sufficient in Australia, 91% of women had a vitamin D level below 9 ng/ml. In our study, no difference was found between the groups according to the veiling status of pregnant women.

Today, the efficacy and safety of vitamin D supplementation are limited. In addition, most studies have been conducted in different ethnic groups, with inconsistent results.

There is insufficient evidence to suggest that low vitamin D levels in early pregnancy are associated with poor pregnancy outcomes. However, our study found a relationship between early pregnancy loss and vitamin D deficiency, and the results may be due to different populations.

Chromosomal anomalies are involved in the etiology of abortion at a rate of 50%, and this rate is 41% in abortions without fetal heartbeat detected in early pregnancy loss. Our study excluded the etiology of the chromosomal anomaly since pregnancies with positive fetal heartbeat at the beginning were included. However, there is no clear result since karyotype is not checked from the abortion materials. Abortions due to maternal reasons such as uncontrolled glycemic, diabetes mellitus, Cushing's syndrome, PCOS were excluded since these patients were not included in the study. Although possible uterine anomalies such as uterine septum are unknown, chemical exposures such as mercury are also unknown. The immunological effect is considered in the unexplained group in the etiology of abortion, and the vitamin D mechanism may be acting through this possible pathway.

CONCLUSION

Vitamin D deficiency is still a long-standing problem for healthcare professionals and the public. Newborns, children, pregnant, and postmenopausal women are at risk. Most human results are the results of animal and laboratory studies and do not show a cause-and-effect relationship. Well-designed clinical studies are few and available information is limited. The differences in the results of the studies are due to the methodology and genetic, ethnic, and racial differences, latitudinal and seasonal differences. Vitamin D deficiency is usually not recognized clinically, but laboratory measurements are easy and treatment is inexpensive. Oral supplementation is the best tolerated and most effective. However, the optimal level of the effect of vitamin D in the reproductive period is not clear. It is still important to determine the most appropriate level and preconceptional starting and the appropriate dose for maximum benefit for mother and baby, especially in the reproductive period and pregnant. Large-scale randomized controlled studies of high quality are needed. By confirming the experimental results of vitamin D deficiency and risks, public health practices can be started.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Education Planning and Coordination Department (Date: 24.01.2014, Decision No: 22).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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I was born in Trabzon in 1985, I have one child. I entered medical school, which has been my dream since I was little and graduated from Marmara University School of Medicine in English in 2010. I have been in the academic area for nearly 13 years since I graduated. I am a specialist in obstetrics and gynecology. My special interests are urogynecology and high- risk pregnancies. I have been editing academic journals and books for many years. I will be happy to take part in projects that I think will benefit the health community and contribute to science.